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# Opioid-Sparing Anesthesia: The Dual Efficacy of Ketamine on Postoperative Pain and Systemic Inflammation Following Spinal Surgery

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**A B S T R A C T**

**Introduction:** Postoperative pain and inflammation after major spinal surgery, such as laminectomy, pose significant challenges to patient recovery and contribute to opioid consumption. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is proposed to have both analgesic and anti-inflammatory properties, positioning it as a key component of an opioid-sparing strategy. This study aimed to evaluate the clinical efficacy of a specific intraoperative ketamine infusion regimen compared to a continuous micro-dose morphine regimen on early postoperative pain and systemic inflammation. **Methods:** This prospective, double-blind, randomized controlled trial included 24 adult patients (ASA I-II) undergoing thoracolumbar laminectomy. Patients were randomly assigned to receive either a continuous intraoperative infusion of ketamine at 10 mcg/kg/minute (n=12) or morphine at 10 mcg/kg/hour (n=12). The primary outcomes were postoperative pain intensity, measured by the Visual Analog Scale (VAS) at 6 and 12 hours, and the systemic inflammatory response, assessed via high-sensitivity C-reactive protein (hs-CRP) levels measured preoperatively and 6 hours postoperatively. **Results:** The study groups were comparable regarding baseline demographic and surgical characteristics ($p>0.05$). At 6 hours postoperatively, the ketamine group reported significantly lower VAS pain scores than the morphine group (mean score of 2.33 ± 0.78 versus 3.83 ± 1.03, respectively; $p=0.001$). This difference was not maintained at 12 hours ($p=0.646$). Critically, the surgically-induced increase in hs-CRP was significantly attenuated in the ketamine group, which showed a mean increase of only 1.43 ± 1.04 mg/L from baseline, compared to a much larger increase of 2.88 ± 1.06 mg/L in the morphine group ($p=0.003$). **Conclusion:** An intraoperative ketamine regimen of 10 mcg/kg/minute is more effective at reducing pain in the immediate 6-hour postoperative period and mitigating the systemic inflammatory response than a continuous micro-dose morphine regimen. These findings underscore ketamine's potent dual-mechanism action, targeting both nociceptive and inflammatory pathways, and strongly support its use in multimodal, opioid-sparing protocols for spinal surgery.

## 1. Introduction

In the landscape of modern medicine, surgical intervention on the spinal column has become a frequent and essential tool for managing a wide array of degenerative, traumatic, and congenital pathologies.[1] Among these procedures, decompressive laminectomy stands out as one of the most common, offering profound neurological relief to a rapidly expanding patient population, a trend driven by the aging of the global population and the rising prevalence of degenerative spine disease. While the technical execution of these surgeries has seen remarkable advancement, the postoperative period remains a landscape fraught with significant physiological

challenges that can profoundly impact patient outcomes. The surgical goal of neural decompression is often met with the iatrogenic reality of significant tissue trauma, which serves as the initiating event for a cascade of adverse physiological responses.[2] The clinical burden of this postoperative phase is substantial. Inadequately managed, the sequelae of spinal surgery lead to a well-documented trajectory of poor outcomes, including prolonged and painful hospital stays, which in turn escalate healthcare costs and diminish institutional efficiency. The pain and physiological stress of recovery act as a direct barrier to early mobilization, a cornerstone of modern enhanced recovery after surgery (ERAS) pathways, thereby increasing the risk of thromboembolic events, pulmonary complications like atelectasis, and generalized deconditioning. However, perhaps the most insidious long-term consequence is the transition from acute, adaptive postsurgical pain to chronic postsurgical pain (CPSP), a maladaptive and often debilitating condition that can afflict a significant portion of patients. CPSP can leave individuals with a legacy of intractable pain, functional limitation, and psychological distress that tragically undermines the very purpose of the initial surgical intervention, making the effective management of the acute postoperative state not just a matter of comfort, but a critical determinant of long-term health and well-being.[3]

A truly effective approach to managing post-laminectomy pain requires a deep understanding of its complex and multifaceted nature. The pain experienced after spinal surgery is not a monolithic entity but rather a composite of distinct pathophysiological processes. The surgical incision, deep muscle dissection, and bone removal create a potent nociceptive pain state, driven by the activation of A-δ and C nerve fibers in response to tissue injury.[4] This is compounded by a significant and often overlooked neuropathic component, which arises from the unavoidable manipulation, retraction, and potential irritation of the spinal nerve roots themselves during the decompression. This mixed pain state is notoriously difficult to manage and creates a powerful and sustained barrage of afferent signals that converge upon the dorsal horn of the spinal cord. Under this intense onslaught, the central nervous system undergoes a profound and clinically crucial transformation known as central sensitization. This process represents a pathological shift in synaptic plasticity, where the spinal cord transitions from a passive conduit of pain signals to an active amplifier. The molecular linchpin of central sensitization is the N-methyl-D-aspartate (NMDA) receptor.[5] During normal pain transmission, this receptor is inactive, its ion channel effectively blocked by a magnesium ion ($Mg^{2+}$). However, the massive and sustained release of the excitatory neurotransmitter glutamate during surgery leads to a powerful depolarization of the postsynaptic neuron via other receptors, chiefly the AMPA receptor. This strong electrical change is sufficient to expel the protective magnesium plug from the NMDA receptor channel. Once unblocked, the NMDA receptor becomes responsive to glutamate, and its activation opens the channel to a massive influx of calcium ($Ca^{2+}$) into the dorsal horn neuron. This calcium surge is the pivotal event that triggers a complex web of downstream intracellular signaling cascades.[6] It activates a host of enzymes, including protein kinase C (PKC) and nitric oxide synthase (NOS), which lead to the phosphorylation of existing receptors (increasing their sensitivity) and changes in gene expression that result in the trafficking of more receptors to the cell surface. This creates a durable state of neuronal hyperexcitability, lowered activation thresholds, and expanded receptive fields, which manifests clinically as the debilitating triad of spontaneous pain, hyperalgesia (exaggerated pain from a painful stimulus), and allodynia (pain from a normally non-painful stimulus). This state of central sensitization is the neurobiological engine that drives intractable postoperative pain and is therefore a primary therapeutic target.

The surgical trauma of a laminectomy also initiates a powerful systemic inflammatory response. Damaged tissues release a flood of endogenous molecules known as damage-associated molecular patterns (DAMPs), which are recognized by the innate immune system and trigger the release of pro-inflammatory cytokines, most notably Interleukin-6 (IL-6). IL-6 enters the systemic circulation and acts as the principal hormonal messenger, instructing the liver to produce acute-phase reactants, the most prominent of which is C-reactive

protein (CRP). High-sensitivity CRP (hs-CRP) is an objective and highly sensitive biomarker of this systemic inflammatory state, and its levels have been strongly correlated with the severity of postoperative pain and the incidence of numerous complications.[7] Contemporary neuroscience has revealed that pain and inflammation are not merely parallel processes but are mechanistically intertwined through the neuro-immune axis. The central nervous system contains its own population of resident immune cells, primarily microglia and astrocytes.[8] The same state of neuronal hyperexcitability that defines central sensitization also serves as a potent activation signal for these glial cells. Once activated, glia transform into a pro-inflammatory phenotype, producing their own inflammatory mediators directly within the spinal cord. This creates a vicious feedback loop where neuronal activity drives glial inflammation, and glial inflammation, in turn, drives further neuronal activity, thereby perpetuating the pain state. Thus, an ideal perioperative intervention should not only block pain signals but also interrupt this destructive cycle of neuro-inflammation.

The historical cornerstone of managing severe postoperative pain has been the use of μ-opioid receptor agonists, such as morphine.[9] While their potent analgesic properties are undeniable, their use is fraught with a host of problems that are incompatible with modern, patient-centered recovery goals. Opioid-related side effects, including respiratory depression, sedation, postoperative nausea and vomiting (PONV), and ileus, are common and directly impede early recovery and mobilization as stipulated by ERAS protocols. Beyond these immediate effects, opioids themselves can contribute to the underlying pathophysiology of pain. Paradoxically, prolonged opioid use can induce a state of hyperalgesia (OIH), and emerging evidence suggests that morphine can directly activate glial cells via Toll-like receptor 4 (TLR4), potentially contributing to the very neuro-inflammatory state it is meant to treat.[10] This, combined with the immense societal burden of the opioid crisis, has created an urgent imperative to develop and implement effective opioid-sparing multimodal analgesic strategies. Within this new paradigm, ketamine has emerged as an agent with a uniquely suitable mechanistic profile. Its primary action as a non-competitive NMDA receptor antagonist allows it to directly target and prevent the induction of central sensitization, a feat that opioids cannot accomplish. By blocking the NMDA receptor channel, ketamine provides a powerful anti-hyperalgesic and neuroprotective effect. Furthermore, a robust body of evidence now confirms that ketamine possesses significant anti-inflammatory properties, including the ability to suppress pro-inflammatory cytokine production and inhibit the activation of the very glial cells that drive neuro-inflammation. This dual mechanism of action—simultaneously targeting neuronal hyperexcitability and neuro-immune activation—positions ketamine as a nearly ideal agent for navigating the complex challenges of the postoperative period.

The novelty of this investigation lies in its integrated approach to test this dual-action hypothesis in a clinically relevant setting. While other studies have examined ketamine as an adjunct, this trial was designed to simultaneously evaluate its impact on both a subjective patient-reported pain outcome (VAS) and an objective physiological marker of systemic inflammation (hs-CRP) in direct comparison to an opioid. The primary aim of this study was to conduct a rigorous, double-blind, randomized controlled trial to compare the effects of a continuous intraoperative infusion of low-dose ketamine versus a continuous micro-dose infusion of morphine on early postoperative pain intensity and the magnitude of the acute inflammatory response in patients undergoing thoracolumbar laminectomy.

## 2. Methods

This investigation was conducted as a prospective, parallel-group, double-blind, randomized controlled trial. The study protocol was designed and executed in strict accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. Formal ethical approval for all study procedures was granted by the Health Research Ethics Committee of Dr. Moewardi Regional General Hospital, Surakarta (Approval No. 1.592/VII/HREC/2025). The trial was also registered with the local institutional review board. All patient

recruitment, surgical procedures, and data collection took place at the Central Surgical Installation of Dr. Moewardi Regional General Hospital between April 2025 and May 2025. The study population consisted of adult patients scheduled for elective thoracolumbar decompression laminectomy under general anesthesia. A systematic screening process was conducted during the preoperative anesthesia assessment to identify eligible candidates.

Inclusion criteria were rigorously applied to ensure a homogenous study population: (1) patients scheduled for elective thoracolumbar decompression laminectomy; (2) age between 18 and 60 years, selected to minimize the confounding effects of advanced age on inflammatory and pain responses; (3) American Society of Anesthesiologists (ASA) physical status I or II, to include patients with no or only mild systemic disease; (4) Body Mass Index (BMI) within the range of 18.6 to 29.9 kg/m², to avoid the known influence of obesity on baseline inflammatory states; and (5) the capacity to understand the study and provide voluntary written informed consent. Exclusion criteria were established to protect vulnerable patients and eliminate significant confounding variables: (1) any known history of hypersensitivity or contraindication to either ketamine or morphine; (2) the presence of severe or unstable systemic disease affecting major organ systems; (3) a diagnosis of malignancy within the past three years or active treatment with chemo- or radiotherapy; (4) a history of chronic pain requiring regular opioid use, to avoid confounding by opioid tolerance or OIH; (5) pregnancy or lactation; and (6) any cognitive or communication barrier that would preclude reliable comprehension and use of the VAS pain scale. Participants were to be withdrawn from the study (drop-out criteria) if any of the following occurred: (1) an acute hypersensitivity reaction to a study drug; (2) a major intraoperative cardiorespiratory adverse event or the need for emergency, non-protocol analgesic administration; (3) a surgical duration that exceeded 180 minutes, to maintain consistency in the degree of surgical stress; (4) the emergence of severe psychomimetic side effects attributable to ketamine that required therapeutic intervention; or (5) the patient's decision to withdraw consent at any time. Every potential participant received a thorough verbal and written explanation of the study's objectives, procedures, timelines, and potential risks and benefits. Written informed consent was meticulously obtained from each patient prior to their enrollment and any study-related activities.

The sample size was determined a priori to ensure adequate statistical power to detect a clinically meaningful difference in the primary outcome of postoperative pain. Based on a review of prior literature investigating analgesia after spinal surgery, a standard deviation (SD) of 1 point on the 10-point VAS was assumed. A difference of 1 VAS point between the groups was designated as the minimal clinically important difference to be detected. With a two-sided significance level ($\alpha$) set at 0.05 and a desired statistical power of 80% ($\beta = 0.20$), the sample size calculation indicated that 12 participants would be required in each group. This yielded a total target enrollment of 24 patients, a number considered both statistically sound for the primary outcome and practically feasible for recruitment within the study's timeframe. To minimize selection bias, participants were randomly allocated in a 1:1 ratio to either the Ketamine Group or the Morphine Group after providing consent. The randomization sequence was generated by an independent biostatistician using a computer-based random number algorithm. Allocation concealment was strictly maintained using sequentially numbered, sealed, opaque envelopes, which were opened only after patient enrollment by a research team member not involved in patient care.

The trial was conducted with a rigorous double-blinding protocol. All involved parties—including the patient, the attending anesthesiologist, the surgical team, the PACU and ward nursing staff, and the data collectors—remained blinded to the treatment allocation throughout the study period. To facilitate this, the study infusions were prepared by an independent anesthesiology resident who had no other role in the study. Ketamine and morphine were diluted in identical 50 mL syringes with normal saline to achieve the same final volume and appearance. Syringes were labeled only with the patient's unique study ID and randomization number. The infusion

pumps were prepared, set, and started by this independent resident, ensuring the clinical team was unaware of the drug being administered. The randomization code was kept secure and was not broken until all data collection and initial analyses were complete. No formal assessment of blinding success was performed, though no instances of apparent unblinding were reported by the clinical teams. Patients received no sedative premedication. Upon arrival in the operating theater, standard ASA monitoring was initiated. Anesthesia was induced and maintained according to a standardized protocol for all participants to ensure consistency. Induction was achieved with intravenous fentanyl (2 mcg/kg) and propofol (1-2.5 mg/kg), with neuromuscular blockade for intubation provided by atracurium (0.5 mg/kg). Anesthesia was maintained with sevoflurane in an air/oxygen mixture, titrated to hemodynamic targets.

Following successful intubation, the prepared study infusion was commenced: Ketamine Group: Received a continuous infusion of ketamine at a rate of 10 mcg/kg/minute. This is a well-established sub-anesthetic dose for intraoperative analgesia. Morphine Group: Received a continuous infusion of morphine at a rate of 10 mcg/kg/hour. This regimen was based on an institutional preference for providing a continuous, low-level opioid background infusion rather than intermittent boluses, and was not designed to be the sole or primary analgesic agent. The study infusion ran continuously throughout the surgery and was stopped at the completion of skin closure. As part of a standardized multimodal regimen, all patients received 1 gram of intravenous paracetamol at the start of skin closure. After reversal of neuromuscular blockade and extubation, patients were transferred to the PACU for immediate postoperative care. Data were recorded on a structured case report form designed for this study: 1. Baseline Data: Preoperative data included demographics (age, gender, BMI) and clinical status (ASA classification). The total duration of surgery was recorded intraoperatively. 2.Primary Outcomes: Postoperative Pain (VAS): The patient's subjective pain intensity was the primary clinical outcome, measured using a 10-point VAS, anchored by "no pain at all" (0) and "the worst pain imaginable" (10). A trained research nurse, blinded to allocation, administered the scale at precisely 6 and 12 hours after the end of surgery; Systemic Inflammation (hs-CRP): The primary biological outcome was the inflammatory response, quantified by hs-CRP levels. Venous blood was drawn at two time points: 12 hours preoperatively (baseline) and 6 hours postoperatively. Samples were analyzed in the central hospital laboratory using a standardized immunoturbidimetric assay. The key outcome was the change (delta) in hs-CRP from baseline. The timing was chosen to capture the early rise in this acute-phase reactant. 3. Secondary Outcome: The need for rescue analgesia (intravenous tramadol) within the first 12 postoperative hours was documented. This was administered based on patient request or a reported VAS score greater than 4.

All statistical analyses were performed using IBM SPSS Statistics, Version 25.0. Statistical significance was defined by a two-tailed p-value of $< 0.05$ for all tests. Descriptive statistics were used to summarize baseline characteristics and outcomes. The Shapiro-Wilk test was used to assess the normality of data distribution. As the primary outcome data (VAS and hs-CRP) were found to be non-normally distributed ($p<0.05$), non-parametric tests were employed for the main comparisons. Baseline characteristics were compared using the independent samples t-test or Chi-square test as appropriate. Differences in VAS and hs-CRP between the two groups were analyzed using the Mann-Whitney U test. The within-group change in hs-CRP for the entire cohort was analyzed using the Wilcoxon signed-rank test. The original analysis plan did not include the calculation of effect sizes or confidence intervals for the primary outcomes.

**3. Results**

A total of 24 patients meeting the eligibility criteria were enrolled and subsequently randomized into the trial. Twelve patients were allocated to the Ketamine Group and twelve to the Morphine Group. All 24 participants successfully completed the assigned study protocol, and data from all patients were included in the final analysis, with no dropouts or protocol violations reported. The demographic and clinical characteristics of the study participants are detailed in Table 1. The

randomization process resulted in two highly comparable groups. There were no statistically significant differences observed between the ketamine and morphine groups in mean age (48.25 ± 10.31 vs. 46.00 ± 8.43 years, p=0.564), mean BMI (22.58 ± 4.29 vs. 23.96 ± 3.59 kg/m², p=0.401), or the distribution of male and female patients (p=1.000). Surgical characteristics were also similar, with no significant difference in the mean duration of surgery (133.17 ± 31.14 vs. 156.75 ± 31.98 minutes, p=0.081). Furthermore, the need for postoperative rescue analgesia was statistically indistinguishable between the groups, with two patients (16.7%) in the ketamine group and three patients (25.0%) in the morphine group requiring it (p=1.000). This baseline homogeneity provides confidence that any observed differences in outcomes are likely attributable to the interventions themselves.

Table 1. Baseline demographic and clinical characteristics.

A comparative summary of study participants at enrollment, stratified by intervention group. The study population consisted of 24 patients undergoing thoracolumbar laminectomy.

| Characteristic | Ketamine Group (n=12) | Morphine Group (n=12) |
|---|---|---|
| Age (years) | 48.25 Mean (SD ±10.31) | 46.00 Mean (SD ±8.43) |
| Body Mass Index (kg/m²) | 22.58 Mean (SD ±4.29) | 23.96 Mean (SD ±3.59) |
| Duration of Surgery (min) | 133.17 Mean (SD ±31.14) | 156.75 Mean (SD ±31.98) |
| Sex Distribution | ♂ 7 (58.3%) ♀ 5 (41.7%) | ♂ 7 (58.3%) ♀ 5 (41.7%) |
| Rescue Analgesia Required | 2 Patients (16.7%) | 3 Patients (25.0%) |

**Note:** There were no statistically significant differences between the groups for any baseline characteristic (p > 0.05 for all comparisons), confirming successful randomization.

As the VAS score data were not normally distributed, the non-parametric Mann-Whitney U test was utilized for the between-group analysis. The comparative results for pain intensity are presented in figure 1. A clear and statistically significant difference emerged at the 6-hour postoperative assessment. The ketamine group reported a mean VAS score of 2.33 ± 0.78, which was substantially lower than the mean score of 3.83 ± 1.03 reported by the morphine group. This difference was highly significant (p=0.001), indicating a more potent analgesic effect of the ketamine regimen in the early postoperative phase. By the 12-hour postoperative mark, pain scores had risen in both groups. The mean VAS score was 5.25 ± 0.87 in the ketamine group and 5.67 ± 1.23 in the morphine group. At this later time point, the difference between the groups was no longer statistically significant (p=0.646), suggesting a convergence of analgesic effect over time. The increase

in pain between 6 and 12 hours was significantly greater in the ketamine group (mean increase of 2.92) compared to the morphine group (mean increase of 1.83), reflecting the shorter duration of action of the initial ketamine infusion (p=0.006).

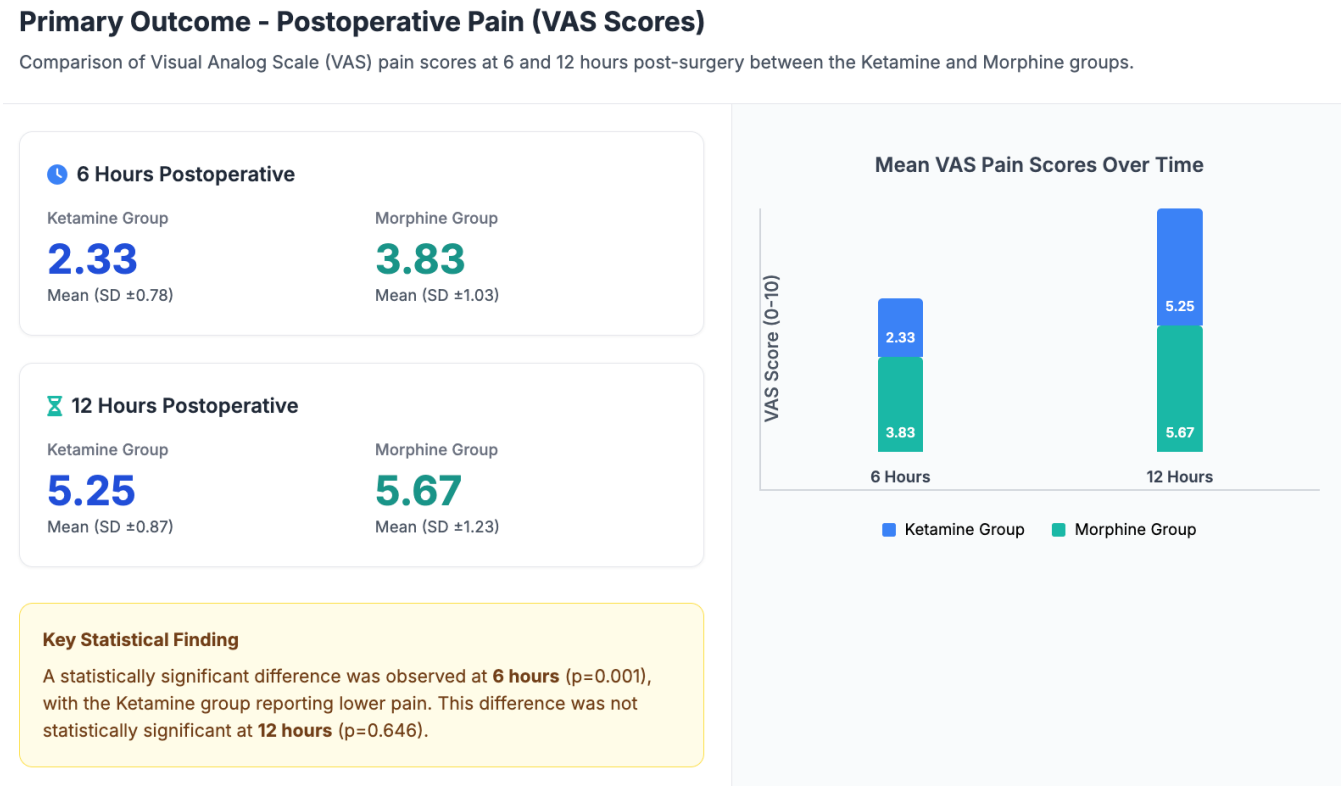


Figure 1. Primary outcome – postoperative pain (VAS Scores).

The analysis of hs-CRP levels is presented in Figure 2. Preoperatively, the baseline hs-CRP levels were low and statistically similar between the Ketamine Group (0.85 ± 0.83 mg/L) and the Morphine Group (1.05 ± 0.72 mg/L), confirming no pre-existing difference in inflammatory status (p=0.386). The surgical procedure itself served as a potent inflammatory stimulus. Across the entire study cohort, there was a highly significant increase in hs-CRP from a preoperative mean of 0.95 ± 0.76 mg/L to a postoperative mean of 3.10 ± 1.81 mg/L (p<0.001, Wilcoxon signed-rank test). The central finding was the significant modulating effect of ketamine on this response. At 6 hours post-surgery, the mean hs-CRP level in the morphine group had risen to 3.93 ± 1.63 mg/L, whereas the level in the ketamine group was significantly lower at 2.28 ± 1.64 mg/L (p=0.015). This effect is further clarified by analyzing the magnitude of the increase (delta hs-CRP) from baseline. The mean increase in hs-CRP in the morphine group was 2.88 ± 1.06 mg/L, more than double the mean increase of 1.43 ± 1.04 mg/L observed in the ketamine group. This difference was statistically significant (p=0.003), providing strong evidence that the intraoperative ketamine regimen markedly attenuated the acute systemic inflammatory response to laminectomy.

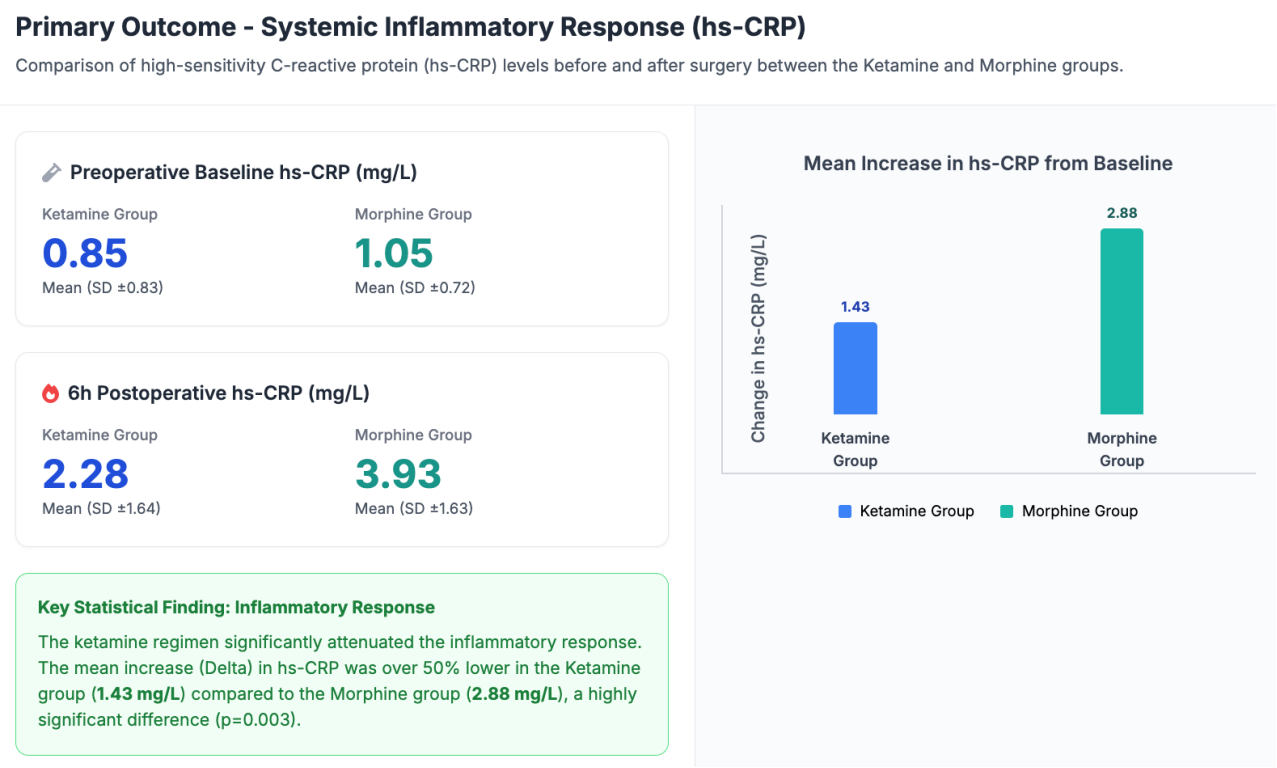


Figure 2. Primary outcome-systemic inflammatory response.

## 4. Discussion

This prospective, randomized trial yielded two clear and statistically significant primary findings. First, an intraoperative regimen of continuous sub-anesthetic ketamine resulted in substantially better pain control in the immediate 6-hour postoperative period compared to a regimen of continuous micro-dose morphine. Second, the ketamine regimen profoundly attenuated the early systemic inflammatory response to surgery, as evidenced by a more than 50% reduction in the rise of hs-CRP.[11] However, a scholarly interpretation of these results must begin with a critical acknowledgment of the study's central methodological feature: the comparison was between two non-equianalgesic drug regimens. The ketamine dose (10 mcg/kg/minute) is a well-established and clinically effective analgesic dose, whereas the morphine dose (10 mcg/kg/hour) is exceptionally low and likely sub-therapeutic for the intense surgical stimulus of a laminectomy. Therefore, this study should not be interpreted as a simple declaration of ketamine's intrinsic pharmacological superiority over morphine. Rather, it should be viewed as a pragmatic trial demonstrating the robust clinical efficacy of a specific, mechanism-targeted ketamine protocol and, conversely, the relative inadequacy of a continuous micro-dose opioid infusion to manage the complex sequelae of spinal surgery.

Figure 3 provides a compelling visual and statistical summary of the study's second primary outcome: the systemic inflammatory response, as quantified by high-sensitivity C-reactive protein (hs-CRP). The selection of hs-CRP as the primary biological outcome measure is a methodologically sound and clinically relevant choice.[12] Surgical trauma, such as the extensive tissue dissection and bone removal involved in a laminectomy, is one of the most potent non-septic triggers of the acute-phase inflammatory response. The body recognizes this sterile injury through the release of damage-associated molecular patterns (DAMPs) from necrotic and stressed cells. These molecules activate resident immune cells, such as macrophages, which in turn unleash a cascade of pro-inflammatory cytokines. Among these, Interleukin-6 (IL-6) is the principal systemic messenger that travels to the liver, where it

serves as the most powerful known stimulus for the synthesis and secretion of acute-phase reactants by hepatocytes. C-reactive protein is the archetypal positive acute-phase protein. Its plasma concentration can increase by several orders of magnitude within hours of an inflammatory stimulus, and its rate of production is directly proportional to the intensity of the ongoing inflammatory process.[13] The use of a high-sensitivity assay (hs-CRP) allows for the precise quantification of even subtle changes in this inflammatory state.

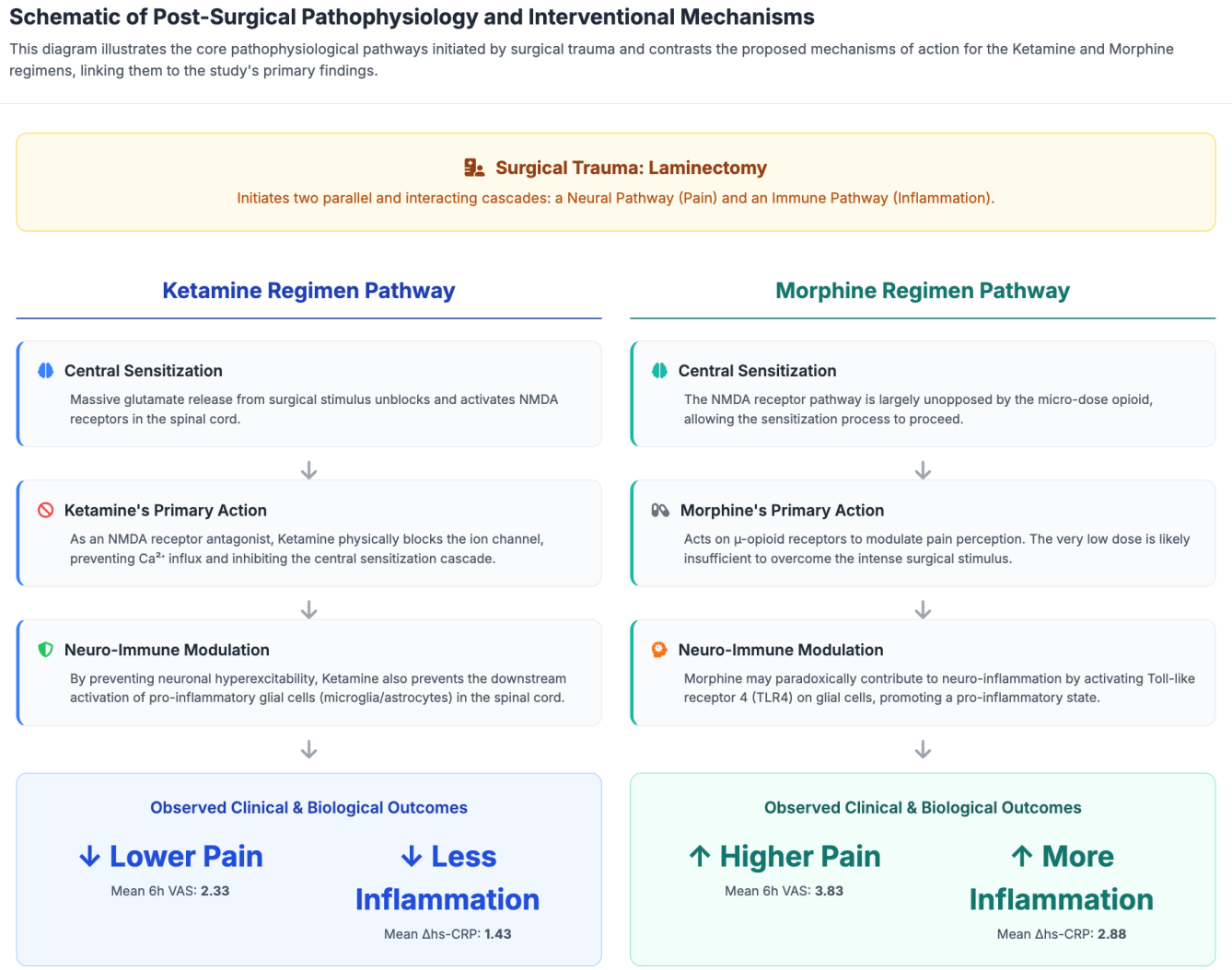


Figure 3. Schematic of post-surgical pathophysiology and interventional mechanisms.

Therefore, hs-CRP serves as an excellent objective, integrated biomarker of the total systemic inflammatory burden imposed by the surgery. Its levels reflect the net effect of the initial tissue injury and any subsequent modulation of that response by therapeutic interventions, making it an ideal tool for investigating the anti-inflammatory properties of the anesthetic agents used in this trial. The first critical piece of information conveyed by Figure 3 is the comparability of the two study groups at baseline. The data clearly show that the preoperative hs-CRP levels were low and statistically indistinguishable between the Ketamine Group (mean 0.85 mg/L) and the Morphine Group (mean 1.05 mg/L). This finding is of paramount importance as it confirms the success of the randomization process in creating two groups with a

similar underlying inflammatory status before any intervention was administered. It effectively eliminates the possibility that any observed postoperative differences were merely a reflection of pre-existing, subclinical inflammation in one group versus the other. This establishes a clean and unbiased foundation upon which the effects of the interventions can be validly compared. Both groups began the surgical journey from the same physiological starting line. As expected, the surgical trauma of laminectomy induced a powerful inflammatory response in all participants. The data show a highly significant increase in hs-CRP levels across the entire cohort when comparing baseline values to the 6-hour postoperative measurement. This confirms that the surgical procedure itself was a sufficient and potent stimulus to activate the systemic acute-phase response. This universal increase serves as the essential backdrop against which the differential effects of the two drug regimens can be assessed. It demonstrates that the key research question is not if inflammation occurs, but rather to what extent it can be modulated by the choice of intraoperative anesthetic. The central and most impactful finding illustrated in Figure 3 is the dramatic divergence in the postoperative hs-CRP response between the two groups. While both groups experienced an increase, the magnitude of this increase was profoundly different. At 6 hours post-surgery, the mean hs-CRP in the Morphine Group had risen to 3.93 mg/L, a nearly four-fold increase from its baseline. In stark contrast, the mean hs-CRP in the Ketamine Group rose to only 2.28 mg/L. This difference is even more clearly illuminated by the analysis of the "Delta hs-CRP"—the mean increase from baseline. The data show that the inflammatory surge in the Morphine Group (a mean increase of 2.88 mg/L) was more than double that observed in the Ketamine Group (a mean increase of 1.43 mg/L). This highly statistically significant difference ($p=0.003$) provides robust, objective evidence that the intraoperative ketamine regimen exerted a powerful anti-inflammatory effect, substantially blunting the systemic stress response to surgery. The profound anti-inflammatory effect of ketamine observed in this study is likely the clinical manifestation of its unique ability to interrupt the neuro-immune feedback loop at its very origin.[14] The intense nociceptive signaling during surgery that drives central sensitization via NMDA receptor activation also serves as the primary trigger for the activation of spinal cord glial cells (microglia and astrocytes). These activated glia, in turn, become miniature cytokine factories, releasing pro-inflammatory mediators that perpetuate neuronal hyperexcitability. Ketamine's primary action as an NMDA receptor antagonist provides a powerful, upstream blockade of this entire cascade. By preventing the initial, excessive neuronal firing and depolarization, ketamine secondarily prevents the downstream activation of these pro-inflammatory glial cells. It effectively quiets the central nervous system, which in turn reduces the central production of cytokines that would otherwise contribute to the systemic inflammatory load. Furthermore, ketamine is known to have direct anti-inflammatory effects on peripheral immune cells, further reducing the overall production of IL-6, the key messenger to the liver. The significantly lower hs-CRP level in the ketamine group is, therefore, a direct and logical consequence of this dual, central and peripheral, anti-inflammatory action. The finding that the morphine group exhibited a significantly more robust inflammatory response is equally fascinating and mechanistically revealing. While traditionally viewed as a pure analgesic, morphine possesses a more complex immunomodulatory profile. Emerging and compelling evidence has identified morphine as an agonist for Toll-like receptor 4 (TLR4), a key pattern-recognition receptor located on the surface of immune cells, most notably microglia in the central nervous system.[15] Activation of TLR4 is a potent pro-inflammatory signal, initiating intracellular cascades that lead to the production of TNF-α and IL-6. Therefore, a paradoxical situation likely occurred in the morphine group: while the drug was administered to treat pain, it may have been simultaneously providing a persistent, low-level pro-inflammatory stimulus to the very glial cells that contribute to pain maintenance and systemic inflammation. This TLR4-mediated glial activation could have directly counteracted morphine's own analgesic effects and contributed to the larger systemic release of IL-6, which then stimulated the liver to produce the significantly higher levels of hs-CRP

observed. In this context, the higher hs-CRP in the morphine group is not simply a failure to be anti-inflammatory; it may be a sign of a subtle but significant pro-inflammatory action, a critical consideration in the modern understanding of opioid pharmacology. Figure 3 does not just show that ketamine is anti-inflammatory; it provides clinical data supporting a sophisticated model where ketamine acts as a modulator of the neuro-immune axis, suppressing a pathological cascade, while morphine, at least in this context, may be an unwitting participant in that same cascade. This highlights a fundamental mechanistic advantage of ketamine that extends far beyond simple analgesia and positions it as a superior agent for maintaining physiological homeostasis during major surgery.

The marked superiority of the ketamine regimen in controlling pain at 6 hours post-surgery is a direct clinical manifestation of its unique pharmacological action at the core of pain pathophysiology.[16] The pain following laminectomy, with its mixed nociceptive and neuropathic character, provides a powerful stimulus for the induction of central sensitization. As previously outlined, this phenomenon of neuronal hyperexcitability is fundamentally dependent on the activation of the NMDA receptor in the dorsal horn. The ketamine regimen directly and preemptively targeted this process. By providing a continuous infusion throughout the period of maximal surgical stimulation, ketamine molecules were consistently available to block the NMDA receptor's ion channel. This action effectively provided a neuroprotective shield, preventing the massive influx of calcium that initiates the downstream cascades of phosphorylation and gene expression responsible for establishing a sensitized state. In essence, the ketamine infusion functioned as a powerful form of preventive analgesia, not just treating the symptom of pain but actively preventing the underlying pathological transformation of the central nervous system. This anti-hyperalgesic action is particularly crucial for managing the neuropathic component of post-laminectomy pain, which is often refractory to conventional opioid analgesics.[17] The morphine regimen, in contrast, was mechanistically ill-equipped to prevent this process. Morphine's primary action, the activation of G-protein coupled μ-opioid receptors, leads to neuronal hyperpolarization and reduced neurotransmitter release. While this is a powerful modulatory effect, it does not directly block the postsynaptic NMDA receptor. At the micro-dose administered in this study, it is highly probable that this modest inhibitory effect was simply overwhelmed by the massive, surgery-induced flood of glutamate in the synaptic cleft. The NMDA receptors were likely still activated, and the central sensitization cascade proceeded largely unchecked, leading to the significantly higher pain scores observed in the morphine group.

The most striking finding of this study is the potent anti-inflammatory effect of the ketamine regimen.[18] The profound attenuation of the hs-CRP response provides compelling clinical evidence for a concept of growing importance in perioperative medicine: the neuro-immune axis. This axis describes the bidirectional communication between the nervous and immune systems, where neural events can directly drive inflammatory responses and vice versa. The results of this trial can be elegantly explained through this framework. The intense neuronal firing and NMDA receptor activation in the spinal cord that drives central sensitization also acts as a powerful trigger for the activation of local immune cells, primarily microglia. Activated microglia are not passive; they become key players in pain maintenance, releasing a host of pro-inflammatory cytokines, including IL-6, directly into the spinal cord. By preventing the initial neuronal hyperexcitability through NMDA receptor blockade, the ketamine regimen likely exerted a powerful secondary effect: it prevented the downstream activation of these pro-inflammatory glial cells, thus quenching a major source of central neuro-inflammation. The story for the morphine group is likely the opposite and provides a fascinating insight into the potential downsides of perioperative opioids. Beyond its action on opioid receptors, morphine has been identified as an agonist for Toll-like receptor 4 (TLR4), a key pattern-recognition receptor found on the surface of immune cells, including microglia. Activation of TLR4 is a potent pro-inflammatory signal. Therefore, it is mechanistically plausible that the continuous micro-dose morphine

infusion, while insufficient to provide adequate analgesia, was nonetheless providing a persistent, low-level pro-inflammatory stimulus to glial cells via TLR4 activation. This could have actively contributed to the neuro-inflammatory state and driven a greater systemic release of cytokines like IL-6, which in turn stimulated the liver to produce the significantly higher levels of hs-CRP observed in the morphine group. In this light, the divergent hs-CRP results are not just an interesting secondary finding; they are a direct reflection of the opposing effects of the two drugs on the neuro-immune axis. Ketamine acted as an anti-inflammatory agent by suppressing a pro-inflammatory pathway (neuronal-glial activation), while morphine may have acted as a pro-inflammatory agent by activating a separate pathway (TLR4).[19] This provides a sophisticated, mechanism-based explanation for the study's biological outcome.

This study's dual-outcome design allows for an integrated interpretation of the findings. The fact that the group with significantly better pain control at 6 hours (ketamine) was also the group with significantly lower systemic inflammation (hs-CRP) is unlikely to be a coincidence. It strongly supports the hypothesis that pain and inflammation are mechanistically linked. The superior analgesia in the ketamine group is likely a product of two synergistic effects: 1) a direct neuro-inhibitory effect by blocking NMDA receptors on neurons, and 2) an indirect analgesic effect by reducing the production of pro-inflammatory cytokines (both centrally from glia and peripherally) that are known to sensitize nociceptive pathways. A formal correlation analysis between individual VAS scores and hs-CRP levels was not performed in this study, but such an analysis in future work would be invaluable for statistically cementing this clinically observed relationship.

The observation that the analgesic benefit of the ketamine regimen had dissipated by the 12-hour mark is a critical finding with direct clinical implications. Ketamine's relatively short half-life means that an intraoperative-only infusion provides powerful but time-limited protection. As the plasma concentration of the drug falls in the postoperative hours, the underlying inflammatory and nociceptive state, though initially dampened, can re-emerge, leading to the observed increase in pain. This finding strongly argues that, for maximum benefit, the protective effects of ketamine should be extended into the postoperative period. Modern perioperative protocols could incorporate a low-dose intravenous ketamine infusion that is continued for the first 12 to 24 hours after surgery. This would provide a continuous mechanistic shield during the period of peak pain and inflammation, potentially leading to dramatically improved recovery trajectories.[20] The findings of this study have profound relevance for ERAS pathways. The ketamine regimen, by providing superior non-opioid analgesia and blunting the systemic stress response, directly aligns with the core goals of ERAS: minimizing physiological derangement, reducing opioid-related side effects, and facilitating early recovery and mobilization. The data strongly support the adoption of intraoperative sub-anesthetic ketamine as a standard of care for major spinal surgery.

The primary strength of this study is its prospective, randomized, and double-blinded design, which minimizes bias and allows for strong causal inference regarding the effects of the tested regimens. The use of both a subjective patient-reported outcome and an objective biological marker provides a comprehensive and scientifically robust assessment. However, the study is not without limitations. The most significant, as has been emphasized, is the non-equianalgesic dosing of the comparator drugs, which limits the interpretation to one of regimen effectiveness rather than pharmacological superiority. The small sample size, while adequately powered for the primary outcome, restricts the generalizability of the findings and the ability to detect differences in less frequent events, such as the need for rescue analgesia. The timing of outcome measurements provided only snapshots of the dynamic postoperative course and did not capture the immediate PACU period or the peak inflammatory response, nor did it allow for any assessment of the transition to chronic pain. Finally, the study population was relatively healthy, and the findings may not apply to patients with more significant comorbidities.

## 5. Conclusion

This prospective, double-blind, randomized controlled trial provides compelling evidence that an intraoperative infusion regimen of sub-anesthetic ketamine (10 mcg/kg/minute) is significantly more effective at controlling pain in the immediate 6-hour postoperative period and substantially attenuating the systemic inflammatory response than a continuous micro-dose morphine infusion regimen (10 mcg/kg/hour) in patients undergoing thoracolumbar laminectomy. The findings are best explained by ketamine's unique dual mechanism, which simultaneously prevents NMDA receptor-mediated central sensitization and modulates the detrimental neuro-immune axis that drives postoperative inflammation. While the analgesic benefits of an intraoperative-only infusion appear to be time-limited, this study robustly supports the integration of ketamine into a modern, multimodal, opioid-sparing anesthetic strategy to improve the quality and trajectory of recovery after major spinal surgery.

## 6. References


1. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain. 2017; 158(3): 463–70.
2. Abd EL-Rahman AM, El Sherif FA. Efficacy of postoperative analgesia of local ketamine wound instillation following total thyroidectomy. Clin J Pain. 2018; 34(1): 53–8.
3. Abd El-Rahman AM, El Sherif FA. Efficacy of postoperative analgesia of local ketamine wound instillation following total thyroidectomy: a randomized, double-blind, controlled clinical trial. Clin J Pain. 2018; 34(1): 53–8.
4. Mohamed SA, Sayed DM, El Sherif FA, Abd El-Rahman AM. Effect of local wound infiltration with ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. Eur J Pain. 2018; 22(5): 951–60.
5. Akhondzadeh R, Rashidi M, Gousheh M, Olapour A, Tasbihi B. Comparison of the ketamine-lidocaine and fentanyl-lidocaine in postoperative analgesia in axillary block in upper limb fractures by ultrasound guidance. Anesth Pain Med. 2019; 9(6): e92695.
6. Zaletskyi BV, Korobko VA, Dmytriiev DV. Clinical case of postoperative anesthesia of a patient by using subanesthetic dose of ketamine in severe abdominal pathology. Pain Med. 2019; 4(1): 61–6.
7. Varas V, Bertinelli P, Carrasco P, Souper N, Álvarez P, Danilla S, et al. Intraoperative ketamine and magnesium therapy to Control postoperative pain after abdominoplasty and/or liposuction: a clinical randomized trial. J Pain Res. 2020; 13: 2937–46.
8. Ali H, Ismail AA, Wahdan AS. Low-dose ketamine infusion versus morphine infusion during abdominoplasty to change the postoperative pain profile. Anesth Pain Med. 2020; 10(6): e108469.
9. Gil LV, Mazzeffi MA, Cai Y, McLeod WW, Porter SB. Reasons for discontinuation of acute postoperative pain ketamine infusions: a retrospective case-control study. Pain Pract. 2021; 21(7): 759–65.
10. Pouldar TM, Maher DP, Betz AW, Wiegers JJ, Friedman JA, Zaidi SS, et al. Adverse effects associated with patient-controlled analgesia with ketamine combined with opioids and ketamine infusion with PCA bolus in postoperative spine patients: a retrospective review. J Pain Res. 2022; 15: 3127–35.
11. Hefni AF, Eldeek AM, Ismael SA, Shaban AR. Comparing effect of adding ketamine versus dexmedetomidine to bupivacaine in Pecs- I I block on postoperative pain control in patients undergoing breast surgery. Clin J Pain. 2022; 38(9): 568–74.
12. Delgado MA, Ferreira LA, Gomes BJDS, Leite IKO, Gomez MV, Castro-Junior C. Preclinical study in a postoperative pain model to

investigate the action of ketamine, lidocaine, and ascorbic acid in reversing fentanyl-induced, non-glutamate-dependent hyperalgesia. Pain Rep. 2023; 8(2): e1062.
13. Doan LV, Li A, Brake L, Ok D, Jee HJ, Park H, et al. Single-dose of postoperative ketamine for postoperative pain after mastectomy: a pilot randomized controlled trial. J Pain Res. 2023; 16: 881–92.
14. Edinoff AN, Askins D, Bobo E, White KL, Eswani Z, Jackson ED, et al. The emerging role of ketamine in acute postoperative pain management. Curr Pain Headache Rep. 2023; 27(9): 387–97.
15. Rashidi M, Mahmoodi K, Akhondzadeh R, Baghbanian R, Jahangiri Mehr F, Safaei Semnani N. Comparison of dexmedetomidine and ketamine in serratus anterior plane block for postoperative pain control in thoracotomy patients: a randomized clinical trial. Anesth Pain Med. 2024; 14(1): e137664.
16. Lucchesi A, Schwenk ES, Silverman ER. Orally administered ketamine and postoperative opioid use in colorectal surgery: a retrospective cohort study. Reg Anesth Pain Med. 2024.
17. Bakhtiari E, Dori MM, Razavi MRD, Yazdi AP, Yazdi AP. Comparison of low-dose ketamine to methadone for postoperative pain in opioid addicts: a randomized clinical trial. Anesth Pain Med. 2024; 19(3): 209–15.
18. Verdonk F, Lambert P, Gakuba C, Nelson AC, Lescot T, Garnier F, et al. Preoperative ketamine administration for prevention of postoperative neurocognitive disorders after major orthopedic surgery in elderly patients: a multicenter randomized blinded placebo-controlled trial. Anaesth Crit Care Pain Med. 2024; 43(4): 101387.
19. Shcheparev IS, Teplykh BA, Fedotova ZN. Use of ketamine infusion for postoperative analgesia in patients undergoing total knee arthroplasty: a prospective randomized single-center study. Reg Anesth Acute Pain Manag. 2025; 19(2): 132–44.
20. Vieira Drumond AL, Nunes Bandeira de Melo L, Ayres Delgado M. Intravenous ketamine infusion for managing chronic postoperative pain after inguinal herniorrhaphy: a case report. J Pain Palliat Care Pharmacother. 2025; 39(3): 403–7.